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Abstract

The objective of this study was to evaluate the safety and tolerability of atorvastatin 10 mg compared with placebo in 2,838 patients with type 2 diabetes and no history of coronary heart disease who were enrolled in the Collaborative Atorvastatin Diabetes Study (CARDS) and followed for 3.9 years.

The percentages of patients experiencing treatment-associated adverse events (AEs), serious AEs and discontinuations due to AEs in the atorvastatin (n=1,428) and placebo (n=1,410) groups were 23.0% *vs.* 25.4%, 1.1% *vs.* 1.1% and 2.9% *vs.* 3.4%, respectively. The most common treatment-associated AEs in the atorvastatin and placebo groups were digestive system-related (8.9% *vs.* 10.0%). All-cause and treatment-associated myalgia were reported in 4.0% and 1.0% of atorvastatin-treated patients, and 4.8% and 1.2% of placebo-treated patients. An analysis of selected AEs by tertiles of baseline low-density lipoprotein (LDL) cholesterol showed no relationship between LDL cholesterol levels and the incidence of myalgia, cancer or nervous system AEs in either treatment group.

Overall, these data demonstrate that atorvastatin 10 mg was well tolerated in patients with type 2 diabetes during long-term treatment.

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Introduction

The efficacy of statins in the prevention of cardiovascular disease (CVD) has been well documented in long-term outcomes trials involving patients with varying degree of cardiovascular risk,[1-7] including patients with type 2 diabetes. The American Diabetes Association and the Joint British Societies' guidelines on the prevention of CVD recommend statin therapy in patients aged over 40 years with diabetes, regardless of their baseline low-density lipoprotein (LDL) cholesterol.[8,9] Atorvastatin has been extensively studied over a broad range of doses.[2,5,6,10-12] However, a thorough evaluation of long-term safety in patients with diabetes has not been published previously.

In the Collaborative Atorvastatin Diabetes Study (CARDS), treatment with atorvastatin 10 mg compared with placebo was associated with a 37% reduction in the incidence of major cardiovascular events (95% confidence intervals 17–52%, p = 0.001), including a 48% reduction in the incidence of stroke, in patients with type 2 diabetes and without elevated LDL cholesterol.[13] The CARDS results confirmed preliminary findings from previous trials that showed significant reductions in cardiovascular end points with statin therapy.[14,15] The objective of the present analysis was to evaluate in detail the safety and tolerability profile of atorvastatin 10 mg compared with placebo among the 2,838 patients in the CARDS safety population. An additional analysis of selected adverse events (AEs) by tertiles of baseline LDL cholesterol was performed to determine whether these AEs occur with greater frequency in patients

with very low levels of LDL cholesterol, and is presented here.

Patients and methods

The CARDS study design, methods, ancillary efficacy end points and baseline characteristics have been described in detail elsewhere.[13,16,17] CARDS was conducted at 132 centres in the UK and Ireland. Study participants were men and women aged 40–75 years with type 2 diabetes and no previous history of CVD. Eligible patients had LDL cholesterol $\leq$ 4.14 mmol/L (160 mg/dL) and triglycerides $\leq$ 6.78 mmol/L (600 mg/dL) and at least one other risk factor (hypertension, retinopathy, microalbuminuria/macroalbuminuria or current smoking). Patients with active liver disease, hepatic dysfunction, severe renal dysfunction or nephrotic syndrome were excluded from the study, as were patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels $\geq$ 1.5 x the upper limit of normal (ULN), plasma creatinine > 150 μmol/L or creatine phosphokinase (CK) $\geq$ 3 x ULN. After the initial screening visit, eligible patients entered a six-week, single-blind placebo period designed to assess compliance with study medication and establish baseline values of study parameters. In the double-blind period, patients were randomised to receive atorvastatin 10 mg or placebo daily. A significant difference in favour of atorvastatin (at $p<0.001$ two-sided) was reported at the second interim analysis, and CARDS was terminated two years earlier than anticipated.

Efficacy and safety end points

The primary end point was the time to first occurrence of the following: acute coronary heart disease (CHD) events (myocardial infarction, including silent infarction, unstable angina, acute CHD death and resuscitated cardiac arrest), coronary revascularisation or stroke. Any untoward medical occurrence, including any procedure-related complication that was not an adjudicated end point and that met the standard definition of an AE, was recorded as such. The only exceptions were deaths due to non-cardiovascular causes, which were reported both as end points and as AEs. AEs were recorded by the investigator at each study visit (months 1, 2, 3 and 6, and every six months thereafter). The severity of the AE, its date of onset and the relationship to study drug were also recorded.

A serious AE (SAE) was defined as an AE that resulted in death; was life-threatening; resulted in hospitalisation or prolongation of hospitalisation, a persistent or significant disability/incapacity or a congenital anomaly/birth defect; or jeopardised the subject and required medical or surgical intervention to prevent one of the outcomes listed above. Occurrences of jaundice, myopathy, as well as elevations in CK to $\geq$ 10 x ULN or in ALT/AST to $\geq$ 3 x ULN, were also reported as SAEs. All SAEs were reported immediately to the sponsor if they occurred at any time during the study through to the last follow-up visit or 30 days after the last dose of the study drug was taken, whichever came later.

Haemoglobin A_{1C} (HbA_{1C}) values were measured at baseline, each annual visit and at the end of study visit. ALT, AST and CK were assessed at all double-blind visits. Levels of CK $\geq$ 10 x ULN or ALT/AST $\geq$ 3 x ULN were recorded as persistent elevations if observed twice within 4–10 days. Descriptive statistics within treatment groups are provided; inferential statistical analyses were not performed.

Table 1. Safety overview for atorvastatin 10 mg compared with placebo

	Atorvastatin (n=1,428)	Placebo (n=1,410)
Patients experiencing $\geq$ 1 AE		
All-cause	1,390 (97.3)	1,376 (97.6)
Treatment-associated	328 (23.0)	358 (25.4)
Discontinuations due to AEs		
All-cause	122 (8.5)	145 (10.3)
Treatment-associated	41 (2.9)	48 (3.4)
Dose interruptions due to AEs		
All-cause	201 (14.1)	172 (12.2)
Treatment-associated	34 (2.4)	23 (1.6)
Patients experiencing serious AEs		
All-cause	421 (29.5)	431 (30.6)
Treatment-associated	15 (1.1)	16 (1.1)

Key: AE = adverse event; Values are number of patients (%)

Patient flow and baseline characteristics

The safety population, defined as the number of randomised subjects who took at least one dose of the study medication, included all 2,838 patients randomised to treatment (1,428 to atorvastatin and 1,410 to placebo).

Demographic characteristics were similar among patients in the atorvastatin and placebo groups; 94% were of white ethnic origin and 68% were men. The mean age was 62 years. Approximately 80% of all patients had hypertension, 30% had retinopathy, approximately 25% were current smokers, and approximately 10% had self-reported microalbuminuria or macroalbuminuria. Overall, 37% of patients had two or more risk factors in addition to diabetes. Concomitant statin therapy was permitted for patients whose LDL cholesterol increased to > 4.65 mmol/L (179 mg/dL) or whose triglycerides increased to > 9.0 mmol/L (800 mg/dL) and for patients who experienced a clinical end point that warranted the introduction of add-in statin therapy. Add-in statin therapy was received by 10.4% of patients in the atorvastatin 10 mg group and 24.8% of patients in the placebo group. The percentage of patients in the placebo group receiving add-in therapy prior to a first primary event was lower than 24.8%.[13]

Results

Overall adverse event profile

An overview of the safety and tolerability profile in atorvastatin- and placebo-treated patients is presented in table 1. The percentage of patients experiencing one or more all-cause and treatment-associated AEs and SAEs was similar between the two groups. The most common treatment-associated AEs in the atorvastatin 10 mg and placebo groups were related to the digestive system (8.9% and 10%) (table

Table 2. Incidence of all-cause and treatment-associated adverse events by body system

	Atorvastatin (n=1,428)	Placebo (n=1,410)
Body as a whole		
All-cause	1,158 (81.1)	1,161 (82.3)
Treatment-associated	97 (6.8)	110 (7.8)
Cardiovascular		
All-cause	587 (41.1)	650 (46.1)
Treatment-associated	22 (1.5)	30 (2.1)
Digestive		
All-cause	714 (50.0)	747 (53.0)
Treatment-associated	127 (8.9)	141 (10.0)
Endocrine		
All-cause	212 (14.8)	214 (15.2)
Treatment-associated	11 (0.8)	10 (0.7)
Haematological/lymphatic		
All-cause	143 (10.0)	144 (10.2)
Treatment-associated	4 (0.3)	2 (0.1)
Metabolic/nutritional		
All-cause	449 (31.4)	464 (32.9)
Treatment-associated	49 (3.4)	50 (3.5)
Musculoskeletal		
All-cause	495 (34.7)	497 (35.2)
Treatment-associated	42 (2.9)	36 (2.6)
Nervous system		
All-cause	510 (35.7)	528 (37.4)
Treatment-associated	45 (3.2)	50 (3.5)
Respiratory		
All-cause	644 (45.1)	623 (44.2)
Treatment-associated	18 (1.3)	23 (1.6)
Skin/appendages		
All-cause	476 (33.3)	474 (33.6)
Treatment-associated	32 (2.2)	30 (2.1)
Special senses		
All-cause	491 (34.4)	528 (37.4)
Treatment-associated	14 (1.0)	13 (0.9)
Urogenital		
All-cause	502 (35.2)	489 (34.7)
Treatment-associated	10 (0.7)	11 (0.8)

Key: Values are number of patients (%)

Table 3. Treatment-associated adverse events occurring in ≥ 0.5% of patients in the atorvastatin 10 mg or placebo groups

	Atorvastatin (n=1,428)	Placebo (n=1,410)
Body as a whole		
Abdominal pain	22 (1.5)	18 (1.3)
Asthenia	8 (0.6)	14 (1.0)
Chest pain	5 (0.4)	8 (0.6)
Headache	31 (2.2)	25 (1.8)
Infection	8 (0.6)	9 (0.6)
Neck pain	7 (0.5)	0
Pain	29 (2.0)	33 (2.3)
Cardiovascular		
Hypertension	8 (0.6)	14 (1.0)
Digestive		
Anorexia	8 (0.6)	4 (0.3)
Constipation	13 (0.9)	16 (1.1)
Diarrhoea	35 (2.5)	33 (2.3)
Dyspepsia	34 (2.4)	37 (2.6)
Flatulence	12 (0.8)	6 (0.4)
Liver function tests abnormal	6 (0.4)	12 (0.9)
Nausea	20 (1.4)	13 (0.9)
Vomiting	8 (0.6)	9 (0.6)
Endocrine		
Diabetes mellitus	11 (0.8)	9 (0.6)
Metabolic/nutritional		
CK increased*	16 (1.1)	16 (1.1)
Hypoglycaemia	7 (0.5)	4 (0.3)
ALT increased*	12 (0.8)	7 (0.5)
Musculoskeletal		
Leg cramps	11 (0.8)	10 (0.7)
Myalgia	14 (1.0)	17 (1.2)
Nervous system		
Dizziness	12 (0.8)	16 (1.1)
Insomnia	9 (0.6)	8 (0.6)
Somnolence	7 (0.5)	7 (0.5)
Respiratory		
Cough increased	9 (0.6)	5 (0.4)
Pharyngitis	3 (0.2)	7 (0.5)
Skin/appendages		
Pruritus	5 (0.4)	7 (0.5)
Rash	14 (1.0)	10 (0.7)

Key: ALT = alanine aminotransferase; CK = creatine phosphokinase; Values are number of patients (%); *Investigator-reported adverse events based on laboratory abnormalities

2). Specific treatment-associated AEs that were commonly reported in the atorvastatin 10 mg and placebo groups, respectively, included diarrhoea (2.5% and 2.3%), dyspepsia (2.4% and 2.6%), headache (2.2% and 1.8%), pain (2.0% and 2.3%) and abdominal pain (1.5% and 1.3%) (table 3).

One hundred and twenty-two (8.5%) patients in the atorvastatin 10 mg group and 145 (10.3%) in the placebo group discontinued treatment because of AEs. The most common reasons for discontinuation in atorvastatin 10 mg- and placebo-treated patients were accidental injury (0.1% and 0.5%), carcinoma (0.3% and 0.6%), pain (0.5% and 0.4%), diarrhoea (0.2% and 0.6%), gastrointestinal carcinoma (0.4% and 0.6%), hypercholesterolaemia (0.1% and 0.9%), hyperlipidaemia (0.1% and 0.6%) and myalgia (0.4% and 0.5%). Relatively small percentages of patients in both groups interrupted the dose of their study drug because of treatment-associated AEs (atorvastatin, 2.4%; placebo, 1.6%) (table 1).

SAEs that met the definition of a clinical end point were included in the efficacy analysis. The SAE, death from any

cause, has been reported previously.[13] In total, 82 people allocated to placebo and 61 who were allocated to atorvastatin died (hazard ratio 0.73, 95% confidence intervals 0.52–1.01, p=0.059). Overall, the incidence of SAEs without regard to causality and the incidence of treatment-associated SAEs were similar in atorvastatin- and placebo-treated patients. The most common SAEs reported in ≥ 1% of patients and occurring at a greater incidence in the atorvastatin group compared with placebo were: accidental injury (3.1% and 2.8%), neoplasm (1.1% and 0.7%), pain (1.2% and 1.1%), vomiting (1.3% and 1.1%) and pneumonia (1.5% and 1.4%). Thirty-six (2.5%) patients in the atorvastatin 10 mg group and 45 (3.2%) in the placebo group died as a result of non-cardiovascular causes, and none of these deaths were considered by the study investigators to be treatment-related.

Muscle-related adverse events

The most common treatment-associated muscle AEs in the atorvastatin 10 mg and placebo groups, respectively, were leg cramps (0.8% and 0.7%) and myalgia (1.0% and 1.2%) (table 4). Myalgia was reported as an SAE in two patients (0.1%) in each treatment group. The onset of myalgia in the atorvastatin-treated patients and placebo-treated patients ranged from seven to 1,932 days, and two to 1,918 days, respectively, after the first dose of the study drug. A complete resolution of myalgia symptoms was observed in 39/57 atorvastatin-treated and 46/67 placebo-treated patients who had at least one myalgia AE. At the time of onset of myalgia symptoms, five patients in the placebo group and none in the atorvastatin 10 mg group were taking add-in statin therapy. Two AEs of myopathy were reported (one in each treatment group). Neither patient was receiving add-in statin therapy at the time and neither case met published criteria for myopathy.[18] CK levels in the atorvastatin-treated patient were 111 U/L at the last measurement prior to AE onset, and 124 U/L at the first measurement after onset; symptoms resolved after discontinuation of atorvastatin therapy.

Single elevations in CK ≥ 10 x ULN occurred in 10 patients (0.7%) in the placebo group and two patients (0.1%) in the atorvastatin 10 mg group; however, six of the 10 placebo patients and both atorvastatin patients had pre-treatment CK levels above the ULN. In patients with normal levels of CK at baseline, single elevations in CK ≥ 10 x ULN were observed in four patients (0.4%) in the placebo group and no patients in the atorvastatin 10 mg group. Persistent elevations in CK ≥ 10 x ULN were not observed in any of these patients. There were no cases of rhabdomyolysis.

Selected adverse events of interest

An analysis of AE reports of alopecia, impotence/erectile dysfunction (ED), deep vein thrombosis and insomnia was performed because these AEs are of special interest to clinicians. Alopecia was reported in 0.2% of patients in the atorvastatin 10 mg group and 0.5% in the placebo group. No alopecia cases were considered to be treatment-related. ED was reported in 4.5% and 5.2% of atorvastatin 10 mg- and placebo-treated patients, respectively (considered treatment-related in 0.1% and 0.4%, respectively). Deep vein thrombosis was observed in 0.8% of atorvastatin 10 mg-treated patients and 1.7% of placebo-treated patients and was considered treatment-related in one patient receiving atorvastatin. Insomnia of any cause was reported in 3.2% and 3.8% of atorvastatin 10 mg- and placebo-treated patients, respectively, and was considered treatment-related in 0.6%.

Table 4. Incidence of all-cause and treatment-associated muscle-related adverse events

	Atorvastatin (n=1,428)	Placebo (n=1,410)
Leg cramps		
All-cause	70 (4.9)	61 (4.3)
Treatment-associated	11 (0.8)	10 (0.7)
Muscle atrophy		
All-cause	4 (0.3)	5 (0.4)
Treatment-associated	1 (0.1)	0
Myalgia		
All-cause	57 (4.0)	67 (4.8)
Treatment-associated	14 (1.0)	17 (1.2)
Myasthenia		
All-cause	18 (1.3)	15 (1.1)
Treatment-associated	3 (0.2)	2 (0.1)
Myopathy		
All-cause	1 (0.1)	1 (0.1)
Treatment-associated	1 (0.1)	0
Myositis		
All-cause	2 (0.1)	2 (0.1)
Treatment-associated	0	1 (0.1)

Key: Values are number of patients (%)

Mean HbA_{1C} values at baseline and last measurement were 7.87% and 8.14% in the atorvastatin group and 7.81% and 8.01% in the placebo group. In a model with adjustment for baseline HbA_{1C} and duration of follow-up, the mean difference between treatment groups at the end of the study was 0.105% (p=0.03).

Hepatic AEs were rare (incidence ≤ 0.1%) in patients receiving atorvastatin 10 mg and included two reports each of liver cirrhosis and hepatomegaly and one report of hepatitis. None of these cases was considered to be treatment-associated. In patients receiving placebo, there were no reports of liver cirrhosis, seven reports of hepatomegaly and three reports of hepatitis. There were five reports of jaundice in the atorvastatin group, one of which was considered treatment-associated, and two reports of jaundice in the placebo group.

Single elevations in ALT ≥ 3 x ULN were observed in 11 patients (0.9%) in the atorvastatin group and eight (0.6%) in the placebo group; persistent elevations were observed in two patients (0.2%) and one patient (0.1%), respectively. Single elevations in AST ≥ 3 x ULN were observed in six patients (0.4%) in the atorvastatin group and four (0.3%) in the placebo group. No persistent elevations in AST ≥ 3 x ULN were observed.

Treatment-associated albuminuria was reported in two

Table 5. Selected adverse events by tertile of baseline LDL cholesterol

	Tertile 1 (LDL cholesterol < 2.75 mmol/L)		Tertile 2 (LDL cholesterol 2.75 to < 3.40 mmol/L)		Tertile 3 (LDL cholesterol ≥ 3.40 mmol/L)	
	Atv (n=475)	Pbo (n=471)	Atv (n=469)	Pbo (n=477)	Atv (n=484)	Pbo (n=461)
LDL cholesterol at one year, mmol/L	1.37 (1.02, 1.67)	2.46 (1.99, 2.91)	1.82 (1.53, 2.15)	3.16 (2.77, 3.53)	2.22 (1.88, 2.57)	3.73 (3.38, 4.16)
AE parameter						
Cancer*	22 (4.6)	24 (5.1)	22 (4.7)	19 (4.0)	25 (5.2)	29 (6.3)
Hypaesthesia	14 (3.0)	19 (4.0)	18 (3.8)	13 (2.7)	10 (2.1)	15 (3.3)
Myalgia	20 (4.2)	21 (4.5)	19 (4.1)	23 (4.8)	18 (3.7)	23 (5.0)
Neuropathy†	41 (8.6)	41 (8.7)	43 (9.2)	32 (6.7)	43 (8.9)	45 (9.8)
Paraesthesia	17 (3.6)	25 (5.3)	20 (4.3)	23 (4.8)	18 (3.7)	24 (5.2)

Key: AE = adverse event; Atv = atorvastatin; LDL = low-density lipoprotein; Pbo = placebo; LDL cholesterol values are median (Q1, Q3); other values are number of patients (%); *All preferred terms which contain carcinoma, melanoma or leukaemia; †All preferred terms which contain neuropathy, neuritis or neuralgia

patients in the atorvastatin group and no placebo group patients. One of these cases was reported as an SAE. Other treatment-associated renal AEs included one report each of kidney failure and nephritis.

There was no difference between the atorvastatin and placebo groups in the incidence of cancer (defined as carcinomas, melanomas and leukaemias). All-cause cancer AEs were reported in 4.8% of atorvastatin-treated patients and 5.1% of placebo-treated patients. Treatment-associated cancer AEs were reported in 0.2% of placebo-treated patients and no atorvastatin-treated patients.

Analysis of adverse events by baseline LDL cholesterol

A post-hoc analysis to determine the safety of low LDL cholesterol was also conducted. Patients were divided into three groups based on the following tertiles of baseline LDL cholesterol: tertile 1, < 2.75 mmol/L; tertile 2, 2.75 to < 3.40 mmol/L; and tertile 3, ≥ 3.40 mmol/L. Incidences of myalgia, cancer and AEs related to the peripheral nervous system were determined across these tertiles. After one year of treatment, atorvastatin-treated patients had a median LDL cholesterol of 1.37 mmol/L in the lowest tertile and 2.22 mmol/L in the highest tertile (table 5). There was no evidence to show that lower LDL cholesterol was associated with a higher incidence of myalgia in the atorvastatin or placebo groups. The incidences of cancer, hypaesthesia, neuropathy and paraesthesia were also similar across tertiles for both treatment groups.

Discussion

Statins are an important component of the medical management of patients with diabetes mellitus.[8,9] Furthermore, atorvastatin has been shown to reduce cardiovascular morbidity in patients with diabetes mellitus, including those without established CHD[13] and those with CHD.[19] Statin treatment of patients with diabetes should be long-term, but some patients with diabetes discontinue statin treatment.[20] This lack of adherence may in part be due to perceived adverse effects of statins.[21] CARDS provides important insights into AEs thought to be associated with statin therapy, and atorvastatin therapy specifically, because the study is double-blind and placebo-controlled, with a duration of nearly four years.

Muscle-related symptoms are attributed commonly to statin therapy, and myopathy has been observed to be dose-related with some statins.[22-24] In CARDS, the overall incidence of treatment-associated muscle-related AEs was relatively low, and was similar in the atorvastatin 10 mg and placebo groups. Although muscle aches are commonly reported in patients receiving statin therapy, the incidence of myalgia in CARDS was similar in atorvastatin- and placebo-treated subjects (4.0% *vs.* 4.8%) and only five of the 67 patients in the placebo group who reported myalgia were receiving add-in statin therapy at the time of symptom onset. These observations are consistent with meta-analyses and recent trials which show that muscle-related AEs in atorvastatin-treated patients are not dose-related.[5,10,11]

Persistent ALT elevations ≥ 3 x ULN were rare in patients receiving atorvastatin (two patients [0.2%]) and placebo (one patient [0.1%]), and no persistent elevations in AST ≥ 3 x ULN were observed. In support of these data, a subgroup analysis of the Treating to New Targets study demonstrated low incidences of persistent elevations ≥ 3 x ULN in ALT and/or AST over 4.9 years in patients with diabetes receiving atorvastatin 10 mg (three patients [0.4%]), and furthermore in those receiving atorvastatin 80 mg (seven patients [0.9%]).[19] These findings in patients with diabetes are consistent with data from the general population in safety meta-analyses of randomised trials of statins[25] and atorvastatin.[10,11]

In lipid-lowering trials in patients with diabetes, limited data suggest that there is no consistent relationship between statin therapy and alterations in glycosylated haemoglobin or other glycaemic parameters. In the current study, small differences in HbA_{1C} concentrations were observed over time in both treatment groups, with a slightly larger difference in

the atorvastatin group. Other studies have also shown small increases in HbA_{1C} following long-term treatment with atorvastatin;[26-28] however, in another large cardiovascular end point trial in patients with diabetes mellitus, the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN), HbA_{1C} concentrations increased by 0.2% among both patients receiving atorvastatin 10 mg and those receiving placebo over four years.[29] There is no known mechanism to explain any changes in glycaemic control with atorvastatin therapy and such a small effect would be more than offset by a substantial reduction of more than a third in the risk of CVD.

The National Cholesterol Education Program Adult Treatment Panel III lipid management guidelines recommend intensive LDL cholesterol lowering (< 1.8 mmol/L) [< 70 mg/dL]) in patients at very high risk for CVD events.[30] However, there have been concerns that lowering cholesterol to very low levels may be associated with adverse outcomes. In CARDS patients receiving atorvastatin 10 mg, LDL cholesterol was not elevated at baseline and it decreased over the course of the study to a median of 1.99 mmol/L (77 mg/dL). There was no evidence to suggest that lowering LDL cholesterol to such levels was associated with an increase in AE incidence. Similar results have been cited in other, high-dose atorvastatin trials in which LDL cholesterol was lowered to an average of 1.6–2.1 mmol/L (60–80 mg/dL).[6,31] The incidence of cancer in the present analysis was similar in atorvastatin 10 mg- and placebo-treated patients and did not vary across tertiles of LDL cholesterol at baseline. Similarly, both the Heart Protection Study involving 20,536 patients[32] and the Cholesterol Treatment Trialists' meta-analysis of 14 trials involving 90,056 patients showed no relationship between LDL cholesterol and cancer incidence.[4]

Current treatment guidelines recommend statin therapy in patients aged 40 years and older with diabetes, regardless of their baseline LDL cholesterol.[8,9] Evidence from the CARDS efficacy analysis and other trials supports these recommendations and indicates that patients with diabetes benefit from statin therapy, especially in the presence of other cardiovascular risk factors. This analysis demonstrates the safety of atorvastatin 10 mg in patients with type 2 diabetes and without elevated LDL cholesterol over a median follow-up period of 3.9 years.

Clinical trial registration

ClinicalTrials.gov Identifier: NCT00327418.

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Conflict of interest statement

CBN, MS and SA were full-time employees of Pfizer Inc. while this study was underway. HMC has received honoraria, has served on an advisory board, and has received research support from Pfizer. DJB has received honoraria from and has served on an advisory board for Pfizer. PND and HAWN have received research support from and have served as consultants for AstraZeneca, Merck Sharp and Dohme, Schering Plough, Solvay Health Care, and Pfizer. GAH has received lecture fees from and has served on an advisory board for Pfizer, GlaxoSmithKline, and AstraZeneca. DAD is a full-time employee of Pfizer Inc. JHF has served as a consultant for and has received research funding from AstraZeneca, Fournier and Pfizer.

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